"On the Physiological Action and Antidotes of Colubrine and Viperine Snake Venoms." By LEONARD ROGERS, M.D., B.S., M.R.C.P., F.R.C.S., Indian Medical Service. Communicated by Dr. A. D. WALLER, F.R.S. Received and read November 19, 1903.

(From the Physiological Laboratory of the London University.)*

(Abstract.)

Part I.—COLUBRINE VENOMS.

The Indian Colubrine snakes other than the Cobra have been little investigated since the classical work of Fayrer, Lauder Brunton and Wall. Their physiological actions are dealt with in this paper.

I. The *Naia Bungarus* or Hamadriad is the largest poisonous snake. The symptoms produced by it are identical with those of Cobra venom, and its toxicity is very similar in degree to it.

Its hæmolytic action is very slight compared to that of the Cobra, its power in this respect being only about one-hundredth that of the latter.

Blood-pressure and respiratory curves of this and the other venoms dealt with in this paper have been taken in the case of cats and rabbits by means of a Gad's manometer connected with a cannula in the carotid artery, and a Sandström recorder connected with a tracheal cannula, with the following results :—

In Experiment I a dose of 5 milligrammes per kilogramme produced paralysis of respiration in $1\frac{1}{2}$ minutes, followed by circulatory failure of a secondary nature in 2 minutes. In Experiment II 1 milligramme per kilogramme produced a temporary stimulation of respiration followed by complete failure in 10 minutes. In Experiment III a very similar result was obtained, while, in addition, it was found that by means of artificial respiration the circulation could be kept going long after total cessation of breathing. In each case the motor end-plates of the diaphragm were paralysed at the end of the experiment, but by means of stimulating the nerve at intervals during the experiment it was found that this paralysis did not take place until after that of the respiratory centre.

The action of Hamadriad venom then, in all respects, resembles that of the Cobra, with the exception that it has very little hæmolytic action.

II. The *Bungarus fasciatus* or Banded Krait, although a large snake, has always been considered the least deadly of its class in India. The symptoms which it produces are very similar to those of the rest of

* A grant in aid of this research was received from the Royal Society.

the class, only in addition it may cause a chronic affection. This difference I find is due to its containing some of the Viperine element in addition to the Colubrine one, and it may thus produce intra-vascular clotting in large doses. The blood-pressure and respiratory tracings show the typical respiratory paralysis of Colubrine venoms, but in addition it causes a marked primary fall of blood pressure, while artificial respiration fails to keep the circulation going, as with the other Colubrine venoms. Heating to 90° C. for a short time greatly lessens this effect on blood pressure and renders artificial respiration much more efficacious, owing to the Viperine element being more readily destroyed by heat than is the Colubrine one. The venom also produces motor end-plate paralysis like the other Colubrines.

III. The *Bungarus cæruleus* or Krait is a small but deadly snake. The symptoms produced by it are identical with those of Cobra venom, and a blood pressure and respiratory tracing shows that it paralyses the central respiratory centre in the same way as the latter. Its action on the phrenic end-plates is, however, somewhat less marked than that of the other Colubrines.

We see, then, that each of these venoms causes death by paralysing the respiratory centre just like Cobra and Sea-snake venoms, but in addition the venom of the Banded Krait has a Viperine element which produces a primary fall of blood pressure, and sometimes intra-vascular clotting, thus resembling the Australian Colubrine snake, the *Pseudechis porphyacus*.

Calmette's antivenin has an undoubted specific action against Cobra venom. It, therefore, becomes a matter of practical importance to ascertain if it is also effective against the other Colubrine and Sea snakes, whose lethal action is identical with that of the Cobra. A series of experiments have been carried out by mixing about ten times a fatal dose of venom with different quantities of the serum for half an hour before injection and noting the results. It was first tested against the common variety of the Cobra, which it neutralised more readily than it did the venom of a less common kind. It acted next best against the Hamadriad or King Cobra, and only a little less so in proportion to its toxicity, against the *Enhydrina bengalensis*, a Sea snake. In the case of the Krait its action was much more feeble, although still distinct, while in that of the Banded Krait it prevented all Colubrine symptoms, if a sufficient dose was used, but the animals died 2—4 days after with symptoms of chronic Viperine poisoning, thus confirming my conclusion that this venom is a mixture of the two elements.

These results are of great interest in showing that the serum has a definite action in neutralising the respiratory paralysing poison of all the Colubrines and the Hydrophidæ, although it will require to be made stronger than it is at present, if it is to be relied on to cure the bites

of those snakes against whose venoms it has the lesser degrees of action, and those which eject a very large quantity of venom. I would suggest that a more generally useful antivenin might possibly be prepared by using a mixture of different Colubrine venoms in the preparation of the serum.

Part II.—The Vipers and Pit-Vipers.

A. *The Viperidæ.*—I. The *Daboia Russellii* produces intra-vascular clotting in small animals, and loss of coagulability of the blood in man, accompanied by hæmorrhages from the bowel, etc. This latter chronic form of poisoning can also be induced in smaller animals by first giving small subcutaneous or intra-venous doses to produce the negative phase of reduced coagulability of the blood, and then larger lethal amounts. As I found that in this way quite rapid deaths without any intra-vascular clotting could be caused by intravenous injections of the venom, accompanied by remarkable primary failure of the circulation, I have made a prolonged investigation of this phenomenon, using the venoms of two Vipers and two Pit-vipers, with results of considerable interest. The direct application of stronger solutions of the venoms than those used in the experiments when applied directly to frogs' hearts, did not stop their action, while in many of the blood-pressure tracings it was evident that the heart continued to beat regularly during and long after the pressure fall. When the pressure fall was sufficiently rapid to stop the respirations by cutting off the blood supply of the medulla, on the occurrence of respiratory convulsions of asphyxial origin the blood pressure was frequently pumped up again in a remarkable manner and the respirations recommenced. Further, the increased excursions of the pulse during the fall of pressure, and the common occurrence of marked Traube-Hering curves, pointed to a relaxation of the blood-vessels of vaso-motor origin.

In order to ascertain if the fall in pressure was due to a central vaso-motor paralysis, further experiments were carried out with Daboia venom. In Experiment VIII the spinal cord of a dog was cut in the cervical region, and artificial respiration kept up. A subcutaneous followed by an intravenous dose of the virus was injected, and no sudden fall of pressure occurred, and the heart continued beating for some minutes, proving that the falls previously obtained were not due to direct action of the venom on the heart. In Experiment IX the circulation in the omentum was observed to undergo a very marked vaso-motor dilatation coincidently with the usual fall in blood pressure, while, after this was complete, no further persistent fall occurred when the cervical cord was cut, proving that complete paralysis of the central vaso-motor centre had already taken place. Lastly, a record of the portal blood volume changes, due to the amount of blood entering the vessels of a large loop of small intestine placed in an oncometer, were

recorded simultaneously with the general blood pressure in the carotid artery, and marked vaso-motor dilatation was observed to take place coincidently with the fall in the general blood pressure, instead of a passive diminution in its volume, which should have taken place if the circulatory failure had been due to a direct action on the heart itself.

That the vaso-motor affection was central, and not peripheral, was shown by the fact that both a small dose of Daboia venom (and also a large one of Cobra) produced contraction of the vessels of the limbs through which blood was transfused after separation from the influence of the central nervous system, while adrenal extract and nicotine caused marked elevation of the blood pressure of a temporary nature after complete paralysis of the central vaso-motor centre, as shown by a stimulation of the central end of the sciatic nerve failing to produce any rise of the general blood pressure.

II. The African Puff-adder. This venom (for which I am indebted to Dr. J. W. W. Stephens) produces intra-vascular clotting like Daboia venom in small animals, but it is much easier to produce the negative phase of lost coagulability, and thus produce death without any clotting with it, than with Daboia venom itself. The blood-pressure and respiratory curves in such cases resemble in every important essential those of Daboia venom without clotting. Adrenal extract has the same effect in raising the fallen pressure, as does nicotine, which was suggested to me by Sir Lauder Brunton. Further, a very marked vaso-dilatation of the portal circulation in a loop of the small intestine, coincidently with the fall in the general blood pressure, was recorded. The Puff-adder venom also had a very marked effect in producing petechial hæmorrhages in the peri- and endo-cardium, and in the mesentery and omentum in particular, which is not at all an important feature of Daboia poisoning.

B. *Crotalidæ*. I. *Crotalus horridus*, or Rattlesnake: I am indebted to Dr. J. Brunton Blaikie for this venom, the hæmorrhagic symptoms produced by which are well known. Blood-pressure and respiratory tracings of the action of this venom showed that the same primary failure of the circulation, as in the former instances, is produced by it, but without any intra-vascular clotting, except rarely at the seat of injection. The failure of the respiration appears to be secondary to that of the circulation, while the very feeble action of strong solutions of the venom directly on the heart will not account for the facts observed, including the pumping-up of the blood pressure with the occurrence of respiratory convulsions and well-marked and persistent Traube-Hering curves, as with the other Viperine venoms. In this case, again, the dilatation of the vessels of the portal circulation, coincidently with the general fall of blood pressure, has been both observed under the microscope and demonstrated with the oncometer.

Further, artificial respiration fails to improve the circulation after respiratory failure, while, in the primary respiratory failure of Colubrine poisoning, it is most effective.

II. *Trimensurus anamallensis*, the Indian representative of the Rattlesnake class has also been examined (thanks to the kindness of Dr. W. Dowson), with precisely similar general results to the others, the same vaso-motor paralysis being induced by a small single intravenous dose without any intravascular clotting, as in the case of the Rattlesnake, while, in larger doses, it kills with intra-vascular clotting like the true vipers. It has much less effect in causing hæmorrhages than either the Rattlesnake or the Puff-adder, but less than the Daboia.

Thus we find from a comparison of the action of these four Vipers that while in the case of the two Pit-vipers a primary circulatory failure, quite independent of any intra-vascular clotting, can be readily induced by a single intra-venous dose of the venoms, the same result can also be brought about in the case of the two true Vipers by first producing the negative phase of reduced coagulability by preliminary small doses of the venoms. Further, there are cases on record of complete loss of clotting power for several days, in which ultimate recovery took place, while the hæmolytic changes, which are produced by all these venoms, are not of lethal intensity. The failure of respiration is always secondary to that of the circulation, while none of these venoms have any marked direct paralysing action on the heart which could account for the circulatory failure.

On the other hand, we find a complete paralysis of the vaso-motor centre in the medulla is common to all these venoms, and will fully account for the lethal effects found, although in some of them the hæmorrhagic effects will greatly aid it. If my conclusion is correct that the essential action of the Viperine poisons as a class is a paralysis of the central vaso-motor centre, just as the Colubrine class paralyse the respiratory centre, then it would appear to be possible to produce an antivenin against the former venom on the same lines as Calmette's serum against the Colubrine class, a mixture of Viperine poisons being used for injections. In the meantime such drugs as adrenal extract and nicotine, together with cardiac tonics, may be of material value in doubtful borderland cases, in keeping up sufficient blood pressure to insure a sufficient supply of blood to the medulla to maintain the respiratory centre working.